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BRIEF REPORTS

Adverse Perinatal Outcomes and Postpartum Multi-Systemic Dysregulation: Adding Vitamin D Deficiency to the Allostatic Load Index

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Abstract *Background* Allostatic load (AL) is an index of multi-system physiological "wear-and-tear," operationalizing emergent chronic disease risk and predicting morbidity and mortality. AL has been proposed as an organizing framework for studying pregnancy outcomes and additional AL biomarkers for the study of maternal health would be valuable. *Objectives* To test whether adverse perinatal outcomes are associated with postpartum AL and if including vitamin D deficiency (serum 25(OH)D < 20 ng/ml) as an additional marker of postpartum AL increases the association. *Methods* The Community Child Health Network is a community-based participatory research network that enrolled women at birth and followed them for 2 years measuring ten biomarkers (body mass index, waist: hip ratio, pulse, systolic and diastolic blood pressures, cortisol slope, c-reactive protein, hgbA1c, HDL, and total cholesterol) at 6 and 12 months postpartum. A composite of four adverse perinatal outcomes (low birth weight, preterm birth, preeclampsia, and gestational diabetes) was collected from medical charts in a sample of 164 women from one site and serum 25(OH)D status was measured 24–39 weeks postpartum in this cohort. *Results* Twenty-nine percent experienced one or more of the four adverse perinatal outcomes. Serum 25(OH)D was significantly inversely correlated with the AL index (Spearman's $r = -0.247$, $p = 0.002$). Logistic regression results adjusting for maternal age and race showed that adverse outcome was significantly associated with higher postpartum AL (OR 1.53 for a 1-unit increase in AL, 95% CI 1.24–1.89). Adding 25(OH)D deficiency as an 11th component to the AL index improved the model fit (Delta $(-2\text{LogL}) = 3.955$, $p = 0.047$), and improved the Akaike information criterion (180.32 vs. 184.27). *Conclusion* Women with adverse perinatal outcomes have higher postpartum AL and adding vitamin D deficiency to the AL index strengthens this association.

Keywords Vitamin D deficiency · 25(OH)D · Allostatic load · Adverse pregnancy or perinatal outcome · Postpartum health

Significance

Higher allostatic load (AL) in the elderly predicts earlier mortality, is associated with adverse health outcomes, and is a better predictor of cardiovascular disease than traditional individual measures. Few AL studies have been conducted with reproductive aged women and vitamin D

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deficiency might be an excellent marker to include in the AL index in this population. This study found that women with adverse perinatal outcomes have higher postpartum AL and adding vitamin D deficiency as an 11th marker to the 10-biomarker AL index improved model fit. Therefore, including vitamin D deficiency in the AL index may be useful in identifying postpartum women at risk of adverse perinatal outcomes in the next pregnancy and potentially at risk for future cardiovascular disease.

Introduction

Included in the objectives of Healthy People 2020 is a goal to reduce maternal illness, pregnancy complications, and rates of low birth weight (LBW) (People 2020). To meet these goals we must better understand the biological mechanisms involved in maternal health, especially how perinatal outcomes develop, in order to identify those at risk. Adverse pregnancy complications and outcomes increase maternal morbidity and infant mortality and cause costly, life-long problems (Creanga et al. 2014). Despite improvements in prenatal care, US rates of adverse perinatal outcomes remain high; specifically, rates are 13% for preterm birth (PTB) (Butler and Behrman 2007); 8.3% for LBW, (Martin et al. 2010) 2–8% for preeclampsia, (Steegers et al. 2010; Redman and Sargent 2005) and 5–9% for gestational diabetes mellitus (DeSisto et al. 2014). These are multi-system disorders associated with poor implantation and placental hypoxia (Sibai et al. 2005), which stimulate the production of pro-inflammatory cytokines by the placenta (Steegers et al. 2010; Ertas et al. 2010; Matthiesen et al. 2005; Ali et al. 2015; Kronborg et al. 2011; Lau et al. 2013). Preeclampsia, for example, is associated with poor fetal growth, leading to LBW and early delivery (Duley 2009) and women who experience adverse perinatal outcomes are at risk for future pregnancy complications and cardiovascular disease (Bellamy et al. 2007; Fraser et al. 2012; Rich-Edwards et al. 2014; Catov et al. 2007).

Allostatic load (AL) represents multi-system physiological "wear-and-tear" and reflects emerging chronic disease risk. It is part of a theoretical framework by which to understand the pathophysiology of diseases due to an accumulating degradation of physiological function (McEwen 1998). By using an AL index representing neuroendocrine, immune, metabolic, and cardiovascular system functioning, numerous studies have demonstrated greater prediction of morbidity and mortality over and above traditional detection methods used in biomedical practice (Juster et al. 2010). Most of the work on AL has been conducted in older adults where higher AL in the elderly predicts earlier mortality, is associated with adverse health outcomes, and is a better predictor of cardiovascular disease (CVD) than traditional individual measures (Seeman et al. 1997, 2010).

AL has also been proposed as a useful concept for pregnancy outcomes and later infant health (Premji 2014; Olson et al. 2015). Increased AL can result when the placenta fails to control metabolic homeostasis (Power and Schulkin 2012). The placenta acts as a regulator of metabolism for the maternal and fetal compartments, acting as a "third brain" during pregnancy. Although pregnancy is a state of low-grade inflammation and insulin resistance, obesity during pregnancy may lead to sustained and inappropriate activation of normally adaptive regulatory circuits as a result of competing and conflicting signaling from adipose tissue and placenta. Recent findings suggest that higher early-pregnancy AL, determined using nine biomarkers, was associated with development of preeclampsia (Hux and Roberts 2015). AL indexed by five biomarkers collected at 26–28 weeks gestation was higher in 123 women who delivered earlier (Wallace and Harville 2013).In a sample of 877 young women who responded to the National Health and Nutrition Examination Survey (NHANES) reproductive-health questionnaire, those with history of small for gestational age (SGA) or PTB had higher AL than did those with normal birth weight outcomes (Hux et al. 2014).

At no other time of a woman's life is there such a dramatic change in the immune and cardiovascular systems that appears to unmask underlying (asymptomatic) metabolic processes (Fraser et al. 2012; Heitritter et al. 2005; Hobel and Arora 2010; Kaaja and Greer 2005). Therefore, additional research is needed focused on AL as related to birth outcomes (Stewart 2006) and on finding new AL biomarkers to assess neuroendocrine functioning (Juster et al. 2010).To our knowledge, vitamin D deficiency has never been included in an AL index. Vitamin D is a unique neurosteroid hormone produced in the skin when exposed to the sun's ultraviolet rays and is also absorbed from various food sources (Zhang and Naughton 2010).Vitamin D regulates placental development and function, promotes tolerance of the fetus(Arora and Hobel 2010) and deficiency is associated with increased rates of preeclampsia and PTB (Arora and Hobel 2010; McCullough 2007; Bodnar et al. 2015). Two recent meta-analyses showed positive associations between vitamin D deficiency and adverse pregnancy outcomes (Aghajafari et al. 2013; Wei et al. 2013). Furthermore, a 2014 "umbrella review" of meta-analyses on associations of vitamin D with a variety of health outcomes concluded that vitamin D is reliably associated with LBW and SGA births, and depression (Theodoratou et al. 2014). As a multi-systemic measure of functioning, vitamin D status might therefore be an excellent marker to include in the AL index in reproductive aged women.

This study is based on the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

(NICHD) funded Community Child Health Network (CCHN), a community-based longitudinal investigation of mostly low income women, not sampled for any specific clinical condition. CCHN followed principles of community-based participatory research (Shalowitz et al. 2009) within each of five community-partnered sites. CCHN's overarching hypothesis was that multi-level stressors lead to higher postpartum AL, which elevates risk for suboptimal outcomes in future pregnancies and the health and development of those children (Dunkel Schetter et al. 2013). The primary purpose of the present study on a subsample of the larger study was to test whether an adverse perinatal outcome was associated with postpartum AL (as measured by ten biomarkers: body mass index, waist:hip ratio, pulse, systolic and diastolic blood pressures, cortisol slope, c-reactive protein, hgbA1c, HDL, and total cholesterol). We hypothesized that women with adverse outcomes would have higher postpartum AL and that the association would be stronger when including vitamin D deficiency (serum 25(OH)D < 20 ng/ml) in the AL index.

Methods

Participants

A total of 2448 mothers were recruited on postpartum units for the larger CCHN study. A nested cohort of women (N = 164) from the Los Angeles site who had adverse perinatal outcome data, AL data and Vitamin D data are included in this study.

Procedures

See Ramey et al. (2015) for CCHN study overview (Ramey et al. 2015). IRB approvals were obtained in all sites. AL indicators were assessed in home visits at 6 and 12 months postpartum. These were: (1) *Body Mass Index (BMI)* was weight (kg) divided by height squared (meters); (2) *Waist:Hip Ratio*: Waist and hip circumferences (centimeters), with high risk clinical cut-off of 0.85;(Circumference and Ratio 2008) (3) *Pulse*: Pulse readings (beats per minute); (4,5) *Systolic and Diastolic Blood Pressures*: Blood pressure readings (mmHg), with clinical cut-offs of 140 for systolic BP and 90 for diastolic BP (WHO criteria); (6) *Cortisol slope*: A "clinical" cut point does not exist, thus values corresponding to the top (flattest) quartile of cortisol slopes were used (−0.01). Flatter slopes are associated with negative health outcomes (Kumari et al. 2009; Matthews et al. 2006, 2011) and earlier mortality(Sephton et al. 2000). Whole blood spots were collected by finger prick. (7) *C-Reactive Protein (hsCRP; mg/L)* was assayed and a pro-inflammatory state was defined as >3.0 mg/l (Rifai et al. 2003). (8) *HgbA1c (%)* with a clinical cutoff of 5.4%, representing pre-diabetes (American Diabetes Association 2012). (9) *HDL* with a clinical cutoff of 40 mg/dL. (10) *Total cholesterol: HDL ratio* used a clinical cutoff value of 5.9(Arsenault et al. 2010).

In the larger study clinical cutoffs (detailed above) as well as quartiles were used to calculate AL. The present study used AL computed for both time points using the "quartile" method by assigning a score of "1" to each component value in the top quartile. HDL was reverse-scored because higher values are advantageous. When at least seven of ten biomarkers were available the sum was scaled to ten by dividing the sum by the total number of non-missing biomarkers and multiplying by ten. AL ranged from 0 to 10 (10 being worse).

Serum 25(OH)D was extracted from spots only in the Los Angeles site of the CCHN network, at either 6 or 12 months postpartum, derived for analysis by highly selective liquid chromatography–tandem mass spectrometry using Zrt laboratory methods, (Eyles et al. 2009; Newman et al. 2009) and modified for automation. The standard cutoff of ≤20 ng/ml was used to define deficiency (Ross et al. 2011).

Perinatal Complications/Outcomes

Pregnancy data were abstracted from the medical records *(coded yes/no)*, including: diagnosed *gestational diabetes mellitus;* diagnosed *preeclampsia; pre-term birth (<37 weeks gestation);* and *low birthweight (<2500 gm)*. A composite of these four adverse perinatal outcomes was created, and women were categorized into two groups (with or without one or more of these).

Other Study Variables

Demographic information was collected by interviews with participants and included *Maternal Age, Education, Marital Status, Race-Ethnicity, Poverty Status, Breast-feeding, and use of Multivitamins and Hormonal Birth Control*.

Statistical Analysis

Descriptive statistics were calculated to characterize participants by demographic and medical variables. Several biomarkers were not normally distributed therefore Spearman's correlations ascertained whether 25(OH)D was significantly correlated with the ten markers that comprise the AL index. Logistic regression models were used to assess the association between adverse perinatal outcome and AL quartile score. We did not test whether high *prenatal* AL predicted adverse pregnancy outcomes but rather whether adverse outcome was followed with higher *postpartum*

AL. Statistically we treated AL as the independent variable even though it was assessed after the pregnancy outcome, the criterion variable. To assess whether 25(OH)D deficiency had the potential to improve the strength of association between the adverse outcome and AL score, 25 (OH)D deficiency was added as a fourth variable to the logistic regression model. We then used the Delta (-2Log-Likelihood) [Delta (-2LogL)] statistic to compare model fit. Finally, we created an 11-biomarker AL score by adding 25(OH)D deficiency as the 11th component and assessed goodness-of-fit by Akaike information criterion (AIC) (Akaike 1987).The model with the minimum AIC value is regarded as the best fitting model (Hooper et al. 2008). Statistical calculations were made using SPSS (20.2) and SAS (9.2), and the 0.05 significance level was used throughout.

Results

Women in the present study (N = 164) were on average 28 years old (SD = 6.6). Approximately half were Latina (55%), 26% were African American and 18% were Caucasian. The average time since delivery was 45 weeks (SD = 13.7) and 50% were primiparous. Participant characteristics were stratified for descriptive purposes by having experienced one or more of four adverse perinatal outcomes (Table 1). In line with rates of adverse perinatal outcomes reported previously in the US (Creanga et al. 2014), 29% (N = 47) experienced one or more of these 4 outcomes. Fifteen percent (N = 24) had PTB, 12% (N = 20) had LBW, 10% (N = 17) had gestational diabetes, and 8% (N = 13) had preeclampsia. Seven of these women also delivered SGA babies, however, none experienced only SGA. Therefore, SGA was not included in the adverse outcome composite. Mean pre-pregnancy and postpartum BMI scores were higher in women who experienced one or more adverse pregnancy outcomes compared to those who did not.

The majority of women had 25(OH)D status measured during April–December (most sunlight) and the mean level of 25(OH)D in the sample was 20.2 ng/ml (SD = 7.2). Approximately half of our sample met criteria for 25(OH)D deficiency (vitamin D ≤ 20 ng/ml). The adverse outcome group had higher rates of 25(OH)D deficiency than those who had no adverse outcomes (68% vs. 48%, p = 0.02), higher use of hormonal birth control (41% vs. 22%, p = 0.06), and lower breastfeeding rates (20% vs. 39%, p = 0.08). Nineteen women experienced more than one outcome (Supplementary Table). They had higher rates of vitamin D deficiency and were more likely to have vitamin D season of measurement in January-March than those with no adverse outcome.

In evaluating the associations of AL biomarkers with Vitamin D (Table 2), 25(OH)D status was significantly, inversely correlated with 7 of the 10 AL biomarkers: pre-pregnancy BMI ($r = -0.37$, $p = 0.0001$), waist/hip ratio ($r = -0.25$, $p = 0.001$), hs-CRP ($r = -0.25$, $p = 0.001$), mean systolic BP ($r = -0.24$, $p = 0.002$), mean diastolic ($r = -0.21$, $p = 0.007$), mean pulse ($r = -0.21$, $p = 0.007$) and HbgA1C ($r = 0.19$, $p = 0.015$).

Logistic regression results, adjusting for maternal age and race, showed that an adverse perinatal outcome was associated with higher postpartum AL (OR 1.53 for a 1-unit increase in AL, 95% CI 1.24–1.89). Adding 25(OH)D deficiency as a separate variable to the logistic regression model improved model fit (Delta (-2LogL) = 5.667, $p = 0.017$). Adding 25(OH)D deficiency as an 11th component to the AL index improved the model fit compared to the 10 component AL index (Delta (−2LogL) = 3.955, $p = 0.047$), and the AIC improved from 184.27 for the 10-biomarker AL model to 180.32 for the 11-biomarker AL model.

Discussion

We found an association between a composite of four key adverse perinatal outcomes and higher postpartum AL measured as a ten component index modeled after existing research (Seeman et al. 1997, 2010). Adding 25(OH)D deficiency to the AL index produced a stronger association with adverse outcome. There is interest in new AL markers(Juster et al. 2010) and our finding suggests that 25(OH)D may have an important role in systemic dysregulation measured by AL. In addition, 25(OH)D's association with seven of the ten AL biomarkers suggests it is part of multi-systemic dysregulation. Normal pregnancy has been likened to a physiological and psychological stress test and the changes in the immune and cardiovascular systems may unmask underlying metabolic dysregulation in some women at risk of disease(Fraser et al. 2012; Heitritter et al. 2005; Hobel and Arora 2010; Kaaja and Greer 2005). Indeed, women with key adverse perinatal complications are at higher risk of developing CVD later in life(DeSisto et al. 2014; Sibai et al. 2005; Ertas et al. 2010; Matthiesen et al. 2005). The present study suggests that a postpartum AL index including 25(OH)D may better predict risk for *future* perinatal outcomes and for CVD, as mediated by adverse perinatal outcomes.

Strengths, Limitations and Future Directions

This study is novel in our decision to add 25(OH)D deficiency to the AL index. Vitamin D deficiency is particularly relevant in reproductive-aged women because of its

Table 1 Demographic and clinical variables stratified by adverse perinatal outcome for descriptive purposes

	Total sample (N = 164)	Controls (N = 117, 71%)	Adverse outcome* (N = 47, 29%)	*p* value
Age (years)	27.8 ± 6.6	27.4 ± 6.7	28.9 ± 6.1	0.17
Married[a]	73(52%)	50/96 (53%)	23/45 (51%)	0.91
Employed (full or part-time)[b]	21(15%)	14/96 (15%)	7/45 (15%)	0.88
Education > high school diploma[c]	61(41%)	44/105 (42%)	17/45 (38%)	0.64
Poverty status[d]				0.75
Poor	71 (43%)	50 (43%)	21 (45%)	
Near poor	45 (27%)	34 (29%)	11 (23%)	
Not poor	48 (29%)	33 (28%)	15 (32%)	
Race/ethnicity				0.76
Caucasian	30 (18%)	20 (17%)	10 (21%)	
African American	42 (26%)	30 (26%)	12 (26%)	
Latina	90 (55%)	65 (56%)	25 (53%)	
Multiracial	2 (1.2%)	2 (1.7%)	0	
Days since delivery	316.1 ± 96.0	319.8 ± 98.6	307.0 ± 89.3	0.44
Primiparous	82 (50%)	56 (48%)	26 (55%)	0.38
Pre-pregnancy BMI	27.6 ± 6.4	26.8 ± 6.2	29.7 ± 6.6	0.01
Postpartum BMI	29.1 ± 6.9	28.2 ± 6.6	31.3 ± 7.1	0.01
Postpartum HBC Use[e]	29 (28%)	15/68 (22%)	14/34 (41%)	0.06
Postpartum multi-vitamin use[f]	14 (13%)	11/70 (16%)	3/35 (9%)	0.38
Breast feeding[f]	34 (32%)	27/70 (39%)	7/35 (20%)	0.08
Vitamin D ng/ml	20.2 ± 7.2	20.8 ± 7.7	18.9 ± 5.7	0.13
Vitamin D < 20 ng/ml	88 (54%)	56 (48%)	32 (68%)	0.02
Season of vitamin D measurement[g]				0.10
April–December	152 (93%)	111 (95%)	41 (87%)	
January–March	12 (7.3%)	6 (5%)	6 (13%)	

Data are N (%) or mean ± standard deviation

Comparison was tested with t-tests, chi square, or Fisher's exact test

Controls were women who did not have any of the adverse perinatal complications of interest in the study

Adverse perinatal outcome includes one or more of the following: low birth weight, preterm birth, preeclampsia or gestational diabetes

*Nineteen (of 47) women experienced more than one adverse outcome (see supplementary table). This subgroup did not statistically differ (from 117 controls) on pre-pregnancy or postpartum BMI, vitamin D levels, or the demographic factors listed above. They did differ on vitamin D deficiency (20% of women who had more than one outcome were vitamin D deficient compared to 8% who were not deficient) and season of vitamin D measurement (40% of women who had more than one outcome delivered in Jan–March compared to 12% who delivered in April–December)

[a]Marital data available for N = 141

[b]Employment data available for N = 141

[c]Education data available for N = 150

[d]Poverty Status: poor = household income below the federal poverty level (FPL)/near poor = household income between 100 and 200% of the FPL/not poor = at least 200% of the FPL

[e]Hormonal birth control (HBC) use data available for N = 102

[f]Multi-vitamin use and breast-feeding data available for N = 105

[g]In the US vitamin D levels peak in late summer (Aug) and trough in late winter (Feb); Kasahara et al. 2013

association with pregnancy complications. For example, in a cohort of 792 women who had preeclampsia, low prenatal 25(OH)D was associated with SGA (Gernand et al. 2014). In addition, women with prenatal vitamin D deficiency were at highest risk of postpartum depression when they had compromised prenatal immune markers in another study (Accortt et al. 2015). We suggest that future AL work in reproductive-aged women should consider the addition of this important biomarker. Including adjustments for hormonal birth control use and breast-feeding in larger samples may also be indicated. A related strength is that many of the high-risk biomarker value

Table 2 Individual biomarker components of allostatic load

Variable	N	Mean	Std dev	Median	Minimum	Maximum	Coefficient*	p-value
Pre-pregnancy BMI	164	27.62	6.43	25.77	18.60	53.35	−0.372	<0.0001
Waist/hip ratio	161	0.883	0.071	0.880	0.724	1.088	−0.254	0.001
Cholesterol ratio	164	4.933	1.602	4.838	1.439	9.560	0.029	0.72
HDL	164	38.7	14.0	36.0	25.0	101.0	0.137	0.079
HbgA1C	164	5.31	0.85	5.20	3.90	12.20	−0.189	0.015
Mean pulse	164	75.8	11.8	75.3	48.7	128.3	−0.210	0.007
Mean systolic	164	108.4	11.4	107.2	88.7	152.3	−0.241	0.002
Mean diastolic	164	73.57	9.99	72.33	53.67	118.33	−0.209	0.007
hs-CRP	164	3.69	3.89	2.15	0.10	25.0	−0.251	0.001
Cortisol slope	92	−0.026	0.025	−0.025	−0.096	0.084	0.049	0.64
AL-10 top quartile score	164	2.41	1.96	2.00	0.00	8.00	−0.247	0.002
Mean 25(OH)D	164	20.2	7.2	19.1	4.1	54.5		

*Spearman correlation coefficients with 25(OH)D

cutoffs used here came from well-characterized and representative existing national data, making the model generalizable beyond this specific population.

There are three main limitations of our study. First, the study was conducted as secondary data analysis, not designed to test a priori hypotheses. Second, women were recruited at birth and we did not test whether high *prenatal* AL predicted adverse pregnancy outcomes but rather whether adverse prenatal and birth outcomes are followed with higher postpartum AL. Importantly, experiencing higher *postpartum* AL may place women at future risk for these outcomes in a subsequent pregnancy. Research can replicate and extend the present findings in larger samples of women recruited in pregnancy and test whether prenatal or preconception AL predicts adverse outcomes. Third, given the sample size, it was not possible to run analyses separately for each adverse perinatal outcome. However, women in our study who experienced more than 1 adverse perinatal outcome had the highest rates of vitamin D deficiency (data not presented), and were more likely to have vitamin D collected during the winter months. Seasonal differences in vitamin D are important to recognize and there is the potential for higher risk of vitamin D deficiency and related complications in cooler climates. However, in winter the oblique angle of the sun is such that few solar UVB photons reach the earth (Holick 2007; Bouillon 2001) even in warmer, sunnier locations like Southern California. Additionally, pre-pregnancy and postpartum BMI were significantly higher in women with an adverse perinatal outcome, a finding worthy of further study. Pre-pregnancy obesity rates are associated with increased incidence of gestational diabetes, preeclampsia, Cesarean, (Gaillard et al. 2013; Chung et al. 2012) postpartum hemorrhage, maternal mortality, (Marshall and Spong 2012) and childhood obesity (Gaillard et al. 2013). Outcomes are exacerbated by excessive weight-gain during pregnancy (Marshall and Spong 2012; Norman and Reynolds 2011).

Clinical Implications

AL theory and assessment allows for early detection of mothers who might be at risk for future health problems, and may help in prevention by targeting earlier interventions. Vitamin D supplementation, for example, is a cost-effective and safe intervention during pregnancy (Hollis et al. 2011) that may benefit the mother's physical health, (Hyppönen 2011; Hobel 2015) mental health, (Accortt et al. 2015; Holick 2015; Anglin et al. 2013) the developing fetus, (Andersen et al. 2015) and the newborn (Kalra et al. 2012; Morales et al. 2012). Indeed, a recent randomized, double-blind, placebo-controlled clinical trial of vitamin D supplementation in 48 pregnant women resulted in significant decreases in serum hs-CRP, fasting plasma glucose, systolic and diastolic BP compared with placebo (Asemi et al. 2013). Thirteen randomized controlled trials (n = 2299) of prenatal vitamin D supplementation to reduce rates of adverse outcomes were recently reviewed in a meta analysis. Vitamin D supplementation during pregnancy was associated with increased circulating 25(OH)D levels, birth weight and birth length, but was not associated with other maternal and neonatal outcomes. The authors discussed that larger, better-designed, RCTs are needed to reach a definitive conclusion (Pérez-López et al. 2015). It is important to note that vitamin D doses were low in some of the included RCTs and we suggest that potential impact of appropriate doses may be likened to folate supplementation for reducing rates of neural tube defects.

Conclusion

This study found an association between adverse perinatal outcomes and postpartum AL and showed that adding vitamin D deficiency to the AL index strengthens this association. Standard AL indices have been used to predict the risk of morbidity and mortality secondary to CVD and stroke. Indeed, many of the AL biomarkers are measures of the effect of inflammation on CVD risk. We argue that adding 25(OH)D deficiency to AL is critical for reproductive aged women because it supports the immune system at the time of implantation, during pregnancy and thereafter (Hayes et al. 2003). AL incorporates genetic, environmental, and behavioral factors that may all influence risk of adverse perinatal and other health outcomes. Future steps include validation in other populations and study of interventions in individuals with higher AL, in addition to vitamin D supplementation, which may inform ways to reduce risk of adverse outcomes in high-risk populations.

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